

Public Comment to the Board of Scientific Counselors
RE: National Toxicology Program Proposed Revisions to the
Process for Preparation of the Report on Carcinogens

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December 15, 2011

Good afternoon and thank you for the opportunity to provide public comment on the draft revisions document being considered by this Board today. My name is Jim Bus. I am a toxicologist and serve as a Director in the Toxicology and Environmental Research and Consulting unit of The Dow Chemical Company. I also have had the privilege to be a member of the Technical Reviews Subcommittee of this BSC in the past and have the highest regard for the important role that it can play in helping NIEHS and NTP be world-class organizations. I am here today because I believe that the BSC needs to ask NTP to go back to the drawing board on these proposed procedures for the Report on Carcinogens.

Given that the National Toxicology Program is globally recognized as an "authoritative body" for its testing and review of environmental chemicals, the NTP Report on Carcinogens classification decisions appropriately carry significant recognition and consequences for future commercial uses and regulatory actions of listed chemicals. For reviews of such consequence, the Obama administration recognized in a 2009 memorandum that government work products of this nature must be transparent, participatory, and collaborative if they are to promote both effectiveness and efficiency regarding reasonable downstream governmental, public and private enterprise actions. More recently, the National Academy of Sciences, in their review of the EPA IRIS Formaldehyde assessment, specifically outlined some fundamental best practices necessary to assure conduct of scientifically credible evidence-based reviews of toxicology-related assessments. The proposed revisions to the Report on Carcinogens preparation process fall considerably short of these objectives and would clearly benefit from additional consultation and comment not only by external parties but also by this Board.

Today I will briefly touch on three areas of concern regarding the proposed draft revisions. The first is that the proposed revisions specifically fail to openly commit to an evidence-based, or weight-of-evidence, examination of the information supporting classification decisions. The second and third concerns are closely related and touch on how the RoC reviews can better benefit from public inputs to the process and to conduct of credible peer review of NTP RoC work products.

Let me turn first to the central necessity for conduct of evidence-based reviews. It is certainly recognized by the members of this Board that toxicology and exposure science is rapidly progressing and becoming

increasingly complex. Such complexity is not to be feared or discouraged, but should be applauded in that new technological advancements, many of which have been the focus of research investigations in your own laboratories, bring insights that can now clarify many of the vexing issues toxicology has faced in the past, and which have often impinged on RoC listing evaluations. These include, for example, improved extrapolations of cross-species observations to human relevance, and defining critical modes of action that shed broad light on interpretation of dose-response relationships and target organ responses. Effective and transparent integration of such information will increasingly become an expectation of many toxicology data evaluations, and particularly so if the desired objective of truly advancing science informed decision-making is to be achieved. The National Academy of Sciences, in their 2011 Formaldehyde report, clearly recognized the value of meeting this challenge, and outlined some key guidance principles by which evidence-based data reviews elevate the overall quality of decision-making. A core foundational element to evidence-based evaluations of complex data sets is the absolute requirement to evaluate such data within an organized framework that assures systematic, transparent, consistent, and accountable evaluation of the data.

The proposed revisions to the RoC process fall well short of this foundational objective. Although the draft speaks of addressing "all information that may bear on a listing decision" and "integrat[ing] the overall body of evidence", it lacks a defined commitment to employing a weight-of-evidence approach to data evaluation. Such evaluations provide a systematic approach to describing how varied data contribute to the questions at hand, which for the RoC, means the considerations leading to potential human carcinogenicity classification. Thus, it is not sufficient to simply "integrate" all data that argue *for* a listing, as is represented by the strength-of-evidence approach used in past Report on Carcinogen reviews and which remains implied in the proposed revisions. Rather, a weight-of-evidence review demands a visible commitment to, and articulation of, standardized data presentation and analysis of all countervailing evidence, and weighs the associated strengths and weaknesses of those data in supporting listing classifications. It is important to note that in recent years systematic frameworks for evaluation of complex toxicology datasets have been developed specifically for facilitation of regulatory evaluation, for example, the International Programme of Chemical Safety framework for mode of action assessments. Development and application of such frameworks is entirely consistent with the significant investments in mode of action research funded by the parent organization of the NTP, NIEHS.

A second key concern regarding the proposed revision is its treatment of external public comment, and how such comment is valued within the review process. Although the process outlines several places where public comment is solicited, NTP is only required to "consider" such inputs, and in no case is required to offer any public response specifically addressing why NTP agrees or disagrees with such comments and how they are treated in RoC documents under review. Equally important, however, is that the proposed revisions offer no guidance as to the timing of when external peer reviewers are provided access to public comment. Since most NTP RoC evaluations are chemical specific, it is very unlikely that peer reviewers will have in-depth knowledge or experience with agents under consideration. My own personal experience as a peer reviewer in such situations is that public comments often provide key insights into potential controversies of data presentation and interpretation, and thus represent productive and essential elements in construction of a quality and

fully informed peer review. Absence of timely access to public comments by peer reviewers, however, marginalizes the potential value of these comments in enhancing the quality of both the RoC documents. In that regard, it is interesting to note that the draft document being reviewed at this meeting was publicly released less than 10 days previously and thus has had no opportunity for public comment other than at this meeting. I also wonder how much, if at all, you were proactively made aware of the specific issues regarding the earlier draft process raised in extensive oral and written public comments. In the public release of this latest draft, NTP certainly made no attempt to identify these issues and indicate why it was responding to some and not others. This is important as an example of how NTP has handled public comments in the past and why further guidance from the BSC is vital.

Finally, the RoC revisions document proposes significant alterations to the peer review process compared to that employed in past RoC assessments. The proposed revisions indicate BSC review will only be sought for the concept document, and its subsequent role in dealing with critical draft RoC monograph is reduced to simply receiving it as information. In place of BSC peer review of the draft RoC monograph, NTP now proposes this review will be implemented by as yet undefined *ad hoc* or standing committees. Importantly, no guidance criteria are provided as to how these peer review panels will be assembled, and particularly if or how public nomination of experts or other inputs to their charge questions will be solicited. In addition, the proposed revisions also eliminate inter-agency peer review of the monograph, and reduce the valuable participation of those experienced groups to simple provision of "inputs" that will only be solicited at the discretion of NTP. If NTP believes specific *ad hoc* or standing committees are indeed best positioned to provide the highest quality peer review of monograph drafts, it should nonetheless be strongly encouraged to retain the BSC as a final check not only for assuring overall quality of specific chemical reviews, but also as an additional arbiter for addressing any potential unresolved controversies associated with assembly of documents, public comments, and the adequacy of NTP responses to peer review panel reports.

In summary, NTP Report on Carcinogen documents are highly influential documents impacting both public and regulatory domains. As such, they are fully deserving of robust document development and review processes that employ well described and standardized efforts resulting in transparent, consistent, and scientifically trustworthy data review and classification decisions. The current draft revisions proposal is premature and incomplete at best, and thus the Board of Scientific Counselors should strongly encourage NTP to:

- go back to the drawing board,
- revise the document to include weight of the evidence, timely issuing of and responses to public comments throughout the process, and an effective oversight role for the BSC, and finally,
- seek appropriate additional inputs to this important process. In that regard, NTP should organize a public workshop in concert with the BSC in order to catalyze interactive dialog between stakeholders on opportunities to best identify effective means for making Report on Carcinogen classifications.

The key importance of the RoC in supporting science informed decisions regarding potential human carcinogens deserves nothing less. Thank you.